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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/728,323	CAPLAN ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2010; 2/29/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-49* is/are pending in the application.

4a) Of the above claim(s) *37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36 and 38-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 February 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/2/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-49 are pending.

Applicant's election of peanut allergen that read on the species of Ara h1, Ara h2, Ara h3 and Ara h6 in the reply filed on June 9, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 37 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

Claims 34-36 and 38-49, drawn to a composition comprising dead *E coli* comprising at least one modified peanut allergen that read on the species of Ara h1, Ara h2, Ara h3 and Ara h6, are being acted upon in this Office Action.

The request under 37 C.F.R. 37 CFR § 1.48(a) filed October 5, 2009 is acknowledged. The inventorship of this application has been changed by adding inventors Hugh A Sampson, Kim H Bottomly, A Wesley Burks, and Howard B Sosin.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/731,375 and provisional application 60/195,035, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The claimed invention is drawn to a composition comprising: dead *E. coli* comprising at least one modified allergen such as Ara h1, Ara h2, Ara h3 or Ara h6 whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen Ara h6 is encapsulated inside the dead *E. coli,* wherein the wild-type protein allergen is peanut allergen Ara h6, the modified peanut allergen lacks an IgE binding site of the wild-type Arah6 peanut allergen sequence, the modified peanut allergen Ara h6 differs from the sequence of the wild-type allergen Ara h6 by one or more amino acid deletions, substitutions, or additions within an IgE binding site of the wild-type allergen Ara h6.

The filing date of instant claims 34-36 and 39-49 is deemed to be the filing date of instant application 10/728,323, which is December 4, 2003. The instant claim 38 is given the priority of 09/731,375 filed December 6, 2000. This is because none of the prior-filed applications mentioned above provides enablement and written support for a composition comprising dead *E coli* comprising at least one modified peanut allergen *Ara h6* that has at least one mutation in an IgE site such that the modified allergen has a reduced ability to bind to or crossed link IgE wherein the modified peanut allergen Ara h6 is encapsulated inside the dead *E coli*.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 2, 2010 has been considered by the examiner.

Specification

The disclosure is objected to because of the following informalities: (1) The "(SEQ ID NO: 2)" in the Brief Description of Figure 5 is now a 10-mer peptide Ala Lys Ser Ser Pro Tyr Gln Lys Lys Thr because the nucleotide sequences of SEQ ID NO: 1-3 as originally presented in the present case have been renumbered as SEQ ID NOs: 81-83, see amendment filed February 29, 2008. The 10-mer peptide cannot span amino acid residues 82-133 of the Ara h1 as shown in Figure 5. (2) Likewise, the same issue occurs in the "(SEQ ID NO. 4)" in the Brief Description of Figure 6 and the "(SEQ ID NO. 6) in the Brief Description of Figure 7. (3) the "SEQ ID NO: 2" at page 49 and page 50 is now a 10-mer peptide, and the SEQ ID NO: 44 is a 15-mer peptide in the Sequence Listing. As such, the position of each of the twenty-two 10-mer peptide with respect to Ara h 1 protein (SEQ ID NO: ?) in Table 4 at page 49 cannot be SEQ ID NO: 2 or SEQ ID NO: 44. (4) The "SEQ ID NO: 4" at page 50, lines 6 and 8 is a 10-mer

peptide in the sequence listing and not the Ara h2 protein as now amended. (5) The "(SEQ ID NO: 6)" at page 50, lines 13 and 15 is inconsistent with the SEQ ID NO: 6 in the sequence listing. Correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Rejections withdrawn

The rejection of claims 34-49 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been obviated by the claims amendment filed February 9, 2010.

Applicant's arguments with respect to claims 34-36, 38-45 and 48-49 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments with respect to claims 46-47 are rejected under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Rejections maintain

Claim rejections under - 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-36 and 38-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34-36 and 43 encompass a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea*

(peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli* and cannot be detected by antibody binding without disrupting the dead *E coli*.

Claim 38 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli* wherein the wild-type allergen is Ara h1, Ara h2, or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3.

Claim 39 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen differs from the sequence of the wild-type allergen by any one or more amino acid deletions, any substitutions, or any addition within any IgE binding site of the wild type peanut allergen.

Claim 40 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) wherein the modified allergen lack any IgE binding site of the wild-type allergen sequence.

Claim 41 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified

allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli*.

Claim 42 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the periplasm of the dead *E. coli*.

Claims 44, 48 and 49 encompass a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* wherein the composition is formulated for rector administration, mucosal administration, or oral administration.

Claim 45 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* and wherein the dead *E. coli* was heat-killed.

Claim 46 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen,

wherein the modified allergen is located in the cytoplasm of the dead *E. coli* and wherein the dead *E. coli* was killed by chemical treatment.

Claim 47 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* and wherein the dead E. coli was killed by iodine, bleach, ozone, or alcohol.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

At the time of filing, applicants are not in possession of any dead *E coli* encapsulated therein any modified peanut allergen Ara h6 whose amino acid sequence has any one or more mutation in any IgE site, any deletions, any substitutions of any amino acid or any addition within any IgE binding site of the wild type peanut allergen Ara h6.

The specification merely discloses a laundry list of allergen including peanut allergen Ara h6. The specification has not identified the IgE binding site within the full-length sequence of Ara h6. There is no information regarding what structural features of the encompassed modified peanut allergen would look like encapsulated in the dead *E coli*. The specification does not describe the common structure of any IgE binding site among the genus of modified peanut allergen Ara h1, Ara h2, Ara h3 and Ara h6. There is no teaching regarding where the IgE sites are in the full length sequence of Ara h6.

The state of the art at the time of filing is such that IgE epitope on allergens are conformational. Aalberse et al (of record, J Allergy Clin Immunol 106: 228-238, 2000; PTO 1449) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular).

Blumental et al (newly cited, in Allergens and Allergen Immunotherapy, 3rd edition, 2004; PTO 892) teach there is no recognized method to distinguish allergic (i.e., those that bind IgE) from non-

allergic molecule (those that do not bind IgE) on a priori structural basis (pages 37-50, the last sentence of the third complete paragraph of page 39, in particular).

Furthermore, it is established in the art that there is a high degree of unpredictability in determining the structure of a given protein because a protein's structure is dependent on its given amino acid sequence and cannot be determined a *priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure.

In this case, there is no specific teaching regarding which amino acids within the full-length sequence of any peanut allergen such as Ara h6 mentioned above when modified by substitution, deletion, addition or combination thereof would reduced its ability to bind to or cross-link IgE. There is no disclosed correlation between structure and function. While general knowledge in the art may have allowed one skill in the art to modify protein by random deletion, substitution, or addition, there is no census in the art about mutation in IgE epitope would led to reduce IgE binding or crosslinking.

For example, Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) teach that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of peanut allergen such

as Ara h6 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating any food allergy.

Even when a precise amino acid within the epitope to be altered is identified, US Patent 6,187,311 (newly cited, February 2001; PTO 892) teaches the choice of what that amino acid should be is also not predictable since substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding (see entire document, col. 3, lines 4-30, in particular).

Likewise, Reese et al (newly cited, J Immunol 175: 8354-8364, 2005; PTO 892) teach it is unpredictable as to which amino acid substitution in shrimp allergen Pen a1 would lead to reduce IgE binding. Reese et al teach that "An interesting and surprising finding was the occasionally increased IgE binding capacity of some mutated epitopes carrying one or two substitutions that originated from tropomyosin sequence even though the unmodified vertebrate tropomyosin sequences did not bind any IgE Abs. An example of this is shown in Fig. 2." Figure 2 provides data wherein a valine at the 5th position of the Pen a 1 epitope 5a was changed to an isoleucine and IgE binding was increased (compare spots 1 and 4 and note that peptide 4 is labeled purple to indicate very strong IgE reactivity). As such, it does not appear that mutating IgE epitopes predictably leads to a reduction in IgE binding activity. Thus one of skill in the art would not be able to immediately envision, recognize or distinguish which unspecified modified peanut allergen listed above has reduced ability to bind to or crossed linked IgE when encapsulated inside dead *E coli* for the claimed composition and would not conclude that applicant is in possession of the claimed genus.

Even assuming the wild type peanut allergen is Ara h1, Ara h2 and Ara h3, the protein sequences of such are not encoded by SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, respectively because SEQ ID NO: 1 to 3 are 10-mer peptides and not nucleotide sequences.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

While the specification provides method to one of skill in the art to screen for modified food allergen with reduced IgE binding, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. Until the modified peanut allergen has been identified by screening, the specification as filed merely ask one of skill in the art to come up with the structure of the claimed modified peanut allergen listed above for the claimed composition for rectal administration, mucosal administration or oral administration.

Because of the unpredictability as to where and what substitutions within which IgE binding sites of any peanut allergen mentioned above when mutated, would result in loss of IgE binding and the described modified peanut allergens Ara hl, Ara h2 or Ara h3 IgE epitopes are not representative of the entire claimed genus of modified peanut allergen such as Ara h6 to suggest applicants would have been in possession of the claimed genus as a whole at the time of filing, the structure associated with function of the claimed modified peanut allergens are not adequately described. Thus the disclosure does not allow one of skill in the art to visualize or recognize the structure of such "modified peanut allergen" required to practice the claimed invention.

Accordingly, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims with respect to the full scope of claims 34-36 and 38-49.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed February 9, 2010 have been fully considered but are not found persuasive.

Applicants' position is that the Examiner is correct that the specification does not explicitly set forth the sequences of all possible mutations to the IgE epitopes found within all of the protein allergens listed in claim 34. However, one of ordinary skill in the art, reading the specification, would readily recognize that the modified protein allergens presented in the specification were merely exemplary and that others would work as well. One of ordinary skill in the art would certainly appreciate that the techniques described in the specification would successfully identify all such substitutions. That is, a skilled person would understand that the present inventors were in *possession* of the invention to the full scope of claim 34.

In response, the law is quite clear that possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. Until the modified peanut allergen such as Ara h6 has been identified by screening, the specification as filed merely ask one of skill in the art to come up with the structure of the claimed modified peanut allergen listed above for the claimed composition for rectal administration, mucosal administration or oral administration.

Claims 34-36 and 38-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising dead *E. coli*. comprising at least one modified peanut allergen protein whose amino acid sequence differs from that of an intact wild-type peanut allergen protein in that at least one IgE epitope has a substitution in the modified peanut allergen protein such that the modified peanut allergen protein has a reduced ability to bind or crosslink IgE as compared with the unmodified peanut allergen protein, wherein: when the wild-type peanut protein is Ara h1, the substitution is in an IgE epitope selected from the group consisting of: an epitope found between amino acids positions listed in Table 4 of Ara h1, when the wild-type peanut protein is Ara h2, the substitution is in an IgE epitope selected from the group consisting of: an epitope found between amino acids positions listed in Table 5 of Ara h2, when the wild-type peanut protein is Ara h3, the substitution is in an IgE epitope selected from the group consisting of: an epitope found between amino acids positions listed in Table 6 of Ara h3 at page 49-50, **does not** reasonably provide enablement for a composition comprising dead *E. coli*. comprising any modified peanut allergen such Ara h1, Arah2 and Arah3 or Ara h6 as set forth in claims 34-36 and 38-49 for treating or *preventing* undesirable allergic reactions and anaphylactic allergic reactions to peanut in a subject. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 34-36 and 43 encompass a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli* and cannot be detected by antibody binding without disrupting the dead *E coli*.

Claim 38 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli* wherein the wild-type allergen is Ara h1, Ara h2, or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3.

Claim 39 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen differs from the sequence of the wild-type allergen by any one or more

amino acid deletions, any substitutions, or any addition within any IgE binding site of the wild type peanut allergen.

Claim 40 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) wherein the modified allergen lack any IgE binding site of the wild-type allergen sequence.

Claim 41 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli.*

Claim 42 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the periplasm of the dead *E. coli.*

Claims 44, 48 and 49 encompass a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* wherein the composition is formulated for rector administration, mucosal administration, or oral administration.

Claim 45 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut)

conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* and wherein the dead *E. coli* was heat-killed.

Claim 46 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* and wherein the dead *E. coli* was killed by chemical treatment.

Claim 47 encompasses a composition comprising: dead *E. coli* comprising any one or more modified peanut allergen such as *Arachis hypogaea* (peanut) vicilin (Ara h1), *Arachis hypogaea* (peanut) (conglutin Ara h2), *Arachis hypogaea* (peanut) (glycinin) Ara h3 and *Arachis hypogaea* (peanut) conglutin homologue (Ara h6) whose amino acid sequence is identical to that of a wild-type allergen, except that the modified allergen has any one or more mutation in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is located in the cytoplasm of the dead *E. coli* and wherein the dead E. coli was killed by iodine, bleach, ozone, or alcohol.

Enablement is not commensurate in scope with claims as how to make any modified peanut allergen such as Ara h1, Ara h2, Ara h3 and Ara h6 encapsulated inside the dead *E. coli* as a composition for treating or preventing peanut allergy.

At the time of filing, the specification discloses only modified peanut allergens Ara h1, Ara h2 and Ara h3 whose IgE site has at least one mutation in an IgE binding site such that the modified peanut allergen has reduced IgE binding, see page 49-50 Table 4-6. The specification discloses only the use of dead *E coli* as a delivery system to treat anaphylactic allergic reactions to peanut in a mouse subject. The methods of killing allergen-producing *E. coli* are heating at temperature ranging from 37 to 95 °C, by ethanol (0.1% to 10%), iodine (0.1% to 10%) and the most reproducible method of killing was heat at 60 °C for 20 minutes and does not denature or proteolyze the recombinant allergen(s) produced by said bacteria, see page 31. The intended use of the claimed pharmaceutical composition is to treat and to

prevent peanut allergy. The specification discloses only modified peanut allergens Ara h1, Ara h2 and Arah3 wherein the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared to wild-type allergen Ara h1, Ara h2 or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, respectively. Further, the specification at page 33 also discloses the levels of allergen release varied and was dependent on the expression vector and protein tested. In general, more Ara h2 was released than Ara h1 and Ara h3 (Ara h2 >>Ara h1>Ara h3). The instant specification at page 34 also discloses that "mice injected with *E. coli* producing Ara h 1 did not give detectable levels of any immunoglobulin to the Ara h 1 allergen and therefore, that data are not shown. Without limitation to theory, we speculate that this may be due to the relatively small amounts of Ara h 1 produced by these cells (see previous discussion). Mice injected with *E. coli* producing Ara h 2 contained relatively high levels of IgG1 and IgG2a. Again, without limitation to the cause, we speculated that this may be due to the amount of Ara h 2 released from these cells (see discussion above). Mice injected with *E. coli* producing Ara h 3 contained relatively high levels oflgG2a (indicative of a Thl-type response) and elicited relatively low levels of IgG1 (indicative of a Th2-type response".

At the time of filing, there is insufficient guidance as to the structure of any *modified peanut allergen* such as Ara h6 having any one or more deletions, substitutions or addition within any IgE binding sites without the amino acid sequence and where such amino acid sequence differs from the undisclosed wild-type allergen sequence.

The specification does not describe the complete structure of any modified peanut allergens encapsulated inside dead *E coli* other than the modified IgE epitopes of peanut allergens Ara h1, Ara h2 and Ara h3 as shown in Table 4, 5 and 6, respectively. The specification does not describe the common structure of any IgE binding site among the genus of modified peanut allergen Ara h1, Ara h2, Ara h3 and Ara h6. There is no teaching regarding where the IgE sites are in the full length sequence of Ara h6.

The state of the art at the time of filing is such that IgE epitope on allergens are conformational. Aalberse et al (of record, J Allergy Clin Immunol 106: 228-238, 2000; PTO 1449) currently available data from crystallographic studies suggest that many IgE epitopes on allergens are conformational (see entire document, abstract, in particular).

As exemplified by the teachings of Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach

modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding. Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* is useful for a composition for treating allergy.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Let alone for prevention of any allergy.

Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of Ara h1 when mutated, would result in loss of IgE binding, in turn, encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm is useful for a composition for treating allergy. Given the unlimited number of modified allergen, modified allergen in any foods, any food such as peanut and the limited in vivo working example, it is unpredictable which undisclosed modified allergen encapsulated inside the dead *E coli* in the claimed composition is effective for treating any allergy. Without the amino acid sequence of any and all modified allergen and the corresponding the cDNA encoding said modified allergen, one of skilled in the art cannot make the recombinant modified allergen encapsulated inside the dead *E coli* for the claimed

composition, let alone for *preventing* allergy in the absence of in vivo working example demonstrating such modified allergen could prevent any allergy.

Chatel et al, of record, teach various factors such as the nature of the allergen, the genetic background of mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the genetics of the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al, of record, teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified allergens, modified food allergens, modified peanut allergens expressed in the dead *E coli* in the claimed composition, there is insufficient *in vivo* working example demonstrating the claimed composition is effective for treating any and all allergy.

Even if the wild-type peanut allergens are limited to Ara h1, and Ara h2 encoded by SEQ ID NO: 81 and 82, respectively, Kleber-Janke et al (Protein Expression and Purification 19: 419-424, 2000; PTO 892) teach the level of expression of peanut allergens using BL21(DE3) *Escherichia coli* host cells depends on the nature of the peanut allergen. Kleber-Janke et al teach cDNA encoding Ara h1 and Ara h2 subcloned into the expression vector pET-16b (Novagen) that uses the T7 RNA polymerase-responsive promoter resulted in *ineffective* expression of Ara h1, Ara h2 and Ara h6 in conventional BL21(DE3) *Escherichia coli* (see page 419, col. 2, first full paragraph, in particular). The reason for the ineffective expression of wild-type Ara h1, Ara h2 and Ara h6 in BL21(DE3) was due to high levels of AGG/AGA in Ara h1, Ara h2 and Ara h6 and the least use arginine codons AGG/AGA in *E. coli* (see abstract, page 419, col. 2, in particular).

Finally, the specification discloses immunizing mice with heat killed *E. coli* expressing three different recombinant peanut allergens resulted in three different outcomes (see page 34 of instant specification). In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of

the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention. Note, amending claim 34 to recite a composition comprising dead *E. coli*. comprising at least one modified peanut allergen protein whose amino acid sequence differs from that of an intact wild-type peanut allergen protein in that at least one IgE epitope has a substitution in the modified peanut allergen protein such that the modified peanut allergen protein has a reduced ability to bind or crosslink IgE as compared with the unmodified peanut allergen protein, wherein: when the wild-type peanut protein is Ara h1, the substitution is in an IgE epitope selected from the group consisting of: an epitope found between amino acids positions listed in Table 4 of Ara h1 (similar language in 11/329,924) would obviate this rejection.

Applicants' arguments filed February 9, 2010 have been fully considered but are not found persuasive.

Applicants' position is that the present claim 34 has been amended to explicitly recite a defined list of allergens. Indeed, Applicant respectfully submits that, at the time when the application was filed, the sequences of many of the allergens recited in claim 34 were known, as were the identities of the IgE epitopes contained within these allergens. To give but one example, p.6-7 of the '978 publication, over which the present application is rejected under § 103, lists published journal articles describing 56 different IgE-binding epitopes from 9 different protein allergens. Thus, it is abundantly clear that identifying the existence and precise location of IgE-binding epitopes is well within the grasp of one of ordinary skill in the art. Moreover, in light of the teachings of the '978 publication, identifying amino acids within such IgE-binding epitopes, mutation of which results in modified IgE-binding ability, was similarly within the grasp of one of ordinary skill in the art.

Moreover, the Examiner states that "the disclosure of a single species usually does not provide an adequate basis to support generic claims" (p. 30 of the Office Action). Fortunately, however, the present specification combined with the level of knowledge and skill in the art provides an abundance of species. As mentioned above, *at least* 56 different IgE-binding epitopes from 9 different protein allergens were known in the art when the present specification was filed, and the specification itself literally exemplifies modification of 37 different IgE-binding epitopes from 3 completely unrelated protein allergens (as argued multiple times during prosecution of this case, the fact that all three of these allergens are found in peanut does not mean that they are similar to one another).

Applicant respectfully submits that, at the time when the application was filed, the sequences of many of the allergens recited in claim 34 were known, as were the identities of the IgE epitopes contained within these allergens. To give but a few representative examples, at the time when the invention was filed, at least 59 different IgE-binding epitopes from one or more different antigens from codfish, egg, cow's milk, hazelnut, peanut, and shrimp (antigens of which are all recited in claim 34) had already been described. And this list is far from exhaustive; indeed, these examples represent a mere sampling of the IgE epitopes that had been described for various food allergens described in claim 34. Thus, it is abundantly clear that identifying the existence *and* precise location of IgE-binding epitopes is well within the grasp of one of ordinary skill in the art. Moreover, in light of the teachings of the present specification, identifying amino acids within such IgE-binding epitopes, mutation of which results in modified IgE-binding ability, was similarly within the grasp of one of ordinary skill in the art.

As was the case in *Wands',* those of ordinary skill in the art can use Applicant's examples and guidance, along with the knowledge and skill available in the art, with a reasonable expectation that they will be able to obtain other modified protein allergens with merely *routine experimentation.* The Examiner is correct that the specification does not explicitly recite all possible mutations to the claimed protein allergens. The Examiner is also correct that the not every variant produced will necessarily have the claimed binding attributes. However, a skilled person, reading the specification, in light of the knowledge and skill available in the art, would understand, indeed would explicitly be *told,* that the working examples are illustrative and instructive, and that the techniques are generalizable to the *precisely-defined* sequences (i. e., IgE-binding epitopes) of other protein allergens with only routine experimentation. Such work is routine, even if laborious.

Contrary to applicants' assertion that the modified peanut allergens encapsulated in the dead *E coli* for the claimed composition is known in the art, the claims encompass a composition comprising: dead *E. coli* comprising any one or more *modified* peanut allergen such as Ara h1, Ara h2, Ara h3 and Ara h6 whose amino acid sequence has any one or more mutation such as deletions, substitutions or additions in any IgE site such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*. The allergen encapsulated in the dead *E coli* is not drawn to any known wild type allergen sequences.

As an initial matter, there is no teaching regarding where the IgE sites are in the full-length sequence of peanut allergen Ara h6. Even assuming the IgE epitopes have been identified, the modified peanut allergen includes any substitution, insertion and/or deletion. There is no guidance as to where and what amino acids to be substituted, deleted and/or added in the IgE epitopes of Ara h6 such that the modified peanut allergen has reduced ability to bind or cross-linked when expressed inside the dead *E coli* as a pharmaceutical composition for rectal administration, mucosal administration or oral administration.

Even when a precise amino acid within the epitope to be altered is identified, US Patent 6,187,311 (newly cited, February 2001; PTO 892) teaches the choice of what that amino acid should be is also not predictable since substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding (see entire document, col. 3, lines 4-30, in particular).

Burk et al (of record, Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) that "there is no obvious position within each peptide (IgE epitope) that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Burk et al teach modifying peanut allergen Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an *increase* in IgE binding.

Stanley *et al* (of record, Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 of wild-type peanut allergen significantly reduced IgE binding while substitution of a serine residue at position 70 leads to an *increase* in IgE binding. Stanley *et al* conclude that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no *obvious position* within each peptide (IgE epitope) that, when mutated, would result in loss of IgE binding.

Likewise, Rabjohn et al (of record, J Clinical Investigation 103(4): 535-542, 1999; PTO 1449) teach modified peanut allergen Ara h3. Rabjohn teach alanine substitution in wild-type peanut allergen Ara h3 at position 308, 309, 310, 311, 312, and 314 led to reduction of IgE binding. However, alanine substitution increases IgE binding at position 304 and 305 within the IgE binding epitope 4 (see page 540, col. 1, Table 2, in particular). Rabjohn et al conclude that "there was no obvious consensus in the type of amino acid that, when mutated to alanine, leads to complete loss or decrease in IgE binding" (see page 540, Mutations at specific residues eliminate IgE binding, in particular). Thus it is unpredictable as to where and what substitutions within which IgE binding sites of peanut allergen such as Ara h6 when

mutated would result in loss of IgE binding, in turn, when encapsulated inside the dead *E coli* such as in the cytoplasm or periplasm, the composition would be useful for treating peanut allergy. Given the lack of description of the structure of modified peanut allergens from species Ara h6, the lack of specific guidance, direction and insufficient working examples, and the high level of predictability in the art as to what the equivalent modified peanut allergen, if any, would be or what function it would have, it would require undue experimentation to make and use the modified peanut allergen within the metes and bounds of the claims that would be reasonably expected to have the desired effect.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-36 and 38-49 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-45 of copending Application No. 10/728,051. Although the conflicting claims are not identical, they are not patentably distinct from each other because issuance of a patent to instant application drawn to a *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in

nature such that the modified allergen such as peanut allergen Ara h1, Ara h2, Ara h3 and Ara h6 has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the modified allergen is located in the cytoplasm or periplasm of the dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol would include the pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: l, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 10/728,051.

Thus the issuance of a patent to instant application (genus) would include the pharmaceutical composition of 10/728,051 (specie). The issuance a patent to copending application 10/728,051 (species) anticipates the claimed composition of instant application (genus).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The examiner acknowledges Applicant's statement that Applicant respectfully refrains from commenting on this rejection until such time as it matures into an *actual* rejection. The rejection is maintained for reasons of record.

New Ground of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-36, 38-40, 43-44 and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US application 2005/0175630 A1 (newly cited, claimed earliest priority to 60/532,786, filed Dec 23, 2003; PTO 892) in view of US Pat No 6,187,311 (newly cited, September 26, 1997; PTO 892) and WO 97/24139 (newly cited, published October 1997; PTO 1449) or Rabjohn et al (of record, J Clin Invest 103(4): 535-542, Feb 1999; PTO 1449).

The US application 2005/0175630 A1 teaches a composition comprising lethally irradiated bacteria such as *E coli* genetically modified to express food allergen such as peanut formulated for mucosal delivery to reduce production of IgE specific for the allergen (see entire document, claims 1 and 17, paragraphs [0090], [0091], [0012], [0120], [0126], [0130], [0328], in particular). The reference dead *E coli* is killed by ionizing radiation (see paragraph [0130], in particular) or by UV radiation (see paragraph [0132], in particular). The reference composition is formulated for mucosal administration such as orally (see claim 1, paragraph [0310], in particular) or rectally (see paragraph [0146], in particular). The advantage of dead bacteria for composition obviates the need for antigen purification, reduced the cost of manufacturing and can be easily and rapidly produced in high quantities inexpensively (see paragraph [0047], in particular).

The cited application does not teach modified peanut allergen such as Ara h1, Ara h2 or Ara h3 whose amino acid sequence is identical to that of wild type except that the modified peanut allergen has at least one mutation in an IgE binding site and the modified allergen is encapsulated inside the dead *E coli*.

The '311 patent teaches modified mite allergen Der f II with reduced IgE binding can be conveniently expressed in *E coli* using the plasmid vector pGEMEX1 from Promega Company. The T7 promoter is used as a high expression promoter and recombinant protein is accumulated (encapsulated) in *E coli* as inclusion bodies located in the cytoplasm (see col. 4, lines 4, line 1-12, in particular).

The WO 97/24139 publication teaches various peanut allergen such as Ara h1 (see entire document, Table 33 at page 169, page 167, sequence in Table 32, in particular), and Ara h2 (see amino acid sequence in Figure 2, in particular). The WO 97/24139 publication further teaches various IgE epitopes within the full-length sequence of Ara h1 (see page 135, Table 22, Fig 23B, in particular) where the IgE epitopes has at least one substitutions such as T92G, R93G, G94A, R95G, E506A in the IgE binding sites that has reduced ability to bind to IgE as compared with the wild-type allergen (see Fig 26 for various amino acid substitutions within the IgE epitope 4 and 17 and compared to wild type (WT), in particular). The WO 97/24139 publication further teaches various IgE epitopes within the full-length sequence of Ara h 2 (see Fig 30, Ara hII, in particular) where the IgE epitope 3 has at least one amino acid substitutions in IgE site such as D62A, P63A, Y64A, P66A such that the modified Ara h2 has reduced ability to bind to IgE as compared to wild type allergen (see Fig 33, in particular). The WO 97/24139 publication teaches three dominant IgE epitopes (aa29-38, aa59-68 and 67-76) in Ara h2 and mutation of these immunodominant epitopes indicate that single amino acid changes result in loss of IgE binding. Both epitopes contained in region aa59-76 contained the amino acid sequence DPYSPS that appears to be necessary for IgE binding (see page 157, lines 14-21, in particular). The publication teaches various portion of Ara h1 such as peptides 1 to 23 (see page 164, Table 28, I particular) and various portion of Ara h2 such as peptides 1 to 6 (see Table 28, I particular). The reference further teaches production of recombinant Ara h I protein in *E coli* (see page 64, lines 3-14, in particular). The WO 97/24139 publication teaches the reference modified Ara h1 or Ara h2 allergen is mutated so that it no longer binds IgE and suggests that it would be useful for treating peanut allergy in human (See claim 32 of the publication, in particular).

Rabjohn et al teach a composition comprising the *E coli* (see page 536, col. 2, Bacterial Expression and purification recombinant Ara h3, in particular) containing therein a modified peanut allergen Ara h3 wherein the modified peanut allergen differs from the wild-type peanut allergen by having more than one amino acid substitutions within the IgE binding epitopes 1-4 for alanine such that the modified peanut allergen Ara h3 has a reduced ability to bind IgE as compared with the wild-type peanut allergen Ara h3 (see page 540, Table 2, Figure 5, in particular). The reference wild type peanut allergen Ara h3 has the same sequence as SEQ ID NO: 3 (see page 537, Fig. 1, in particular). Rabjohn et al teach the cDNA encoding the modified peanut allergen Ara h3 is useful for treating peanut allergy (see paragraph bridging page 541-2, in particular). The reference Ara h3 has the amino acid sequence as set forth in GenBank Accession number AF093541.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a composition comprising dead *E coli* comprising modified peanut allergen by substituting the modified mite allergen Der f II encapsulated inside the *E coli* of the '311 patent for the modified peanut allergen Ara h1 or Ara h2 that has at least one substitution in an IgE binding site such that the modified allergen has reduced IgE binding or crosslinking as compared with the wild-type Ara h1 or Ara h2 as taught by the WO 97/24139 publication or the modified peanut allergen Ara h3 that has reduced IgE binding or crosslinking as taught by Rabjohn et al and then render the *E coli* dead by lethal irradiation as taught by the US application 2005/0175630 A1.

One having ordinary skill in the art would have been motivated with the expectation of success to use dead *E coli* that have produced modified allergen as a delivery vehicle because dead *E coli* as delivery vehicle obviates the need for antigen purification, reduced the cost of manufacturing and can be easily and rapidly produced in high quantities inexpensively as taught by the US application 2005/0175630 A1 (see paragraph [0047], in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to use non-secreted *E coli* as allergen delivery system because it is common sense to shield the highly anaphylactic peanut allergen as taught by the WO 97/24139 publication or Rabjohn et al from the immune system until it is engulfed by antigen presenting cells known to any one of ordinary skill in the immunology art.

One having ordinary skill in the art would have been motivated with the expectation of success to modified peanut allergen Ara h1 or Ara h2 because mutated peanut allergen that has reduced IgE binding would be useful for treating highly anaphylactic peanut allergy in human as taught by the WO 97/24139 publication (See claim 32 of the publication, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to modified peanut allergen Ara h3 because modified peanut allergen Ara h3 that has reduced IgE binding as compared with the wild-type peanut allergen Ara h3 has the therapeutic potential for treating peanut allergy as taught by Rabjohn et al (see abstract, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, combining prior art elements of modified peanut allergens and expression of modified peanut allergens in *E coli* as inclusion bodies located in the cytoplasm according known method would yield predictable results.

In this case, simple substitution of one known allergen for another allergen in the dead *E coli* would yield predictable results.

Since the use of dead *E coli* that have produced encapsulated modified allergen of interest as a delivery vehicle is desirable and has been predictable and known at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention. Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Claims 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US application 2005/0175630 A1 (newly cited, claimed earliest priority to 60/532,786, filed Dec 23, 2003; PTO 892) in view of US Pat No 6,187,311 (newly cited, September 26, 1997; PTO 892) and WO 97/24139 publication (published October 1997; PTO 1449) or Rabjohn et al (of record, J Clin Invest 103(4): 535-542, Feb 1999; PTO 1449) as applied to claims 34-36, 38-40, 43-44 and 48-49 mentioned above and further in view of US Pat No 6,004,815 (newly cited, issued December 21, 1999; PTO 892).

The combined teachings of the US application 2005/0175630 A1, the '311 patent and the WO 97/24139 publication or Rabjohn et al have been discussed supra.

The invention in claim 45 differs from the teachings of the references only in that the composition wherein the dead *E coli* was heat-killed.

The invention in claim 47 differs from the teachings of the references only in that the composition wherein the dead *E coli* was killed by alcohol, iodine, bleach or ozone.

The '815 patent teaches the use of dead microorganisms such as *E coli* as a delivery vehicle to deliver any antigen of interest to antigen presenting cells (see entire document, abstract, col. 4, lines 26-45, in particular). The '815 patent teaches various means of killing bacteria known in the art such as killing by chemical, i.e., methanol, UV irradiation or heat to preserve the microbial membrane and cell wall to retain the expressed foreign antigen or allergen (see col. 4, lines 38-50, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to kill *E coli* that has produced modified peanut allergen Ara h1, Ara h2 or Ara h3 of interest of the US application 2005/0175630 A1, the '311 patent and the WO 97/24139 publication or Rabjohn et al by means of heat or methanol known to skill in the art as taught by the '815 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to kill *E coli* bacteria by means of heat or methanol to preserve the microbial membrane and cell wall to retain the expressed foreign antigen of interest as taught by the '815 patent (see col. 4, lines 38-50, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to use dead *E coli* that have produced food allergen as a delivery vehicle because dead *E coli* eliminates the inherent risk of live bacteria *in vivo* as taught by the '815 patent (see col. 15, lines 24-57, col. 16, lines 29-40, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to use non-secreted *E coli* as allergen delivery system because it is common sense to shield the highly anaphylactic peanut allergen as taught by the WO 97/24139 publication or Rabjohn et al from the immune system until it is engulfed by antigen presenting cells known to any one of ordinary skill in the immunology art.

One having ordinary skill in the art would have been motivated with the expectation of success to modified peanut allergen Ara h1 or Ara h2 because mutated peanut allergen that has reduced IgE binding

would be useful for treating highly anaphylactic peanut allergy in human as taught by the WO 97/24139 publication (See claim 32 of the publication, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to modified peanut allergen Ara h3 because modified peanut allergen Ara h3 that has reduced IgE binding as compared with the wild-type peanut allergen Ara h3 has the therapeutic potential for treating peanut allergy as taught by Rabjohn et al (see abstract, in particular).

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over US application 2005/0175630 A1 (newly cited, claimed earliest priority to 60/532,786, filed Dec 23, 2003; PTO 892) in view of US Pat No 6,187,311 (newly cited, September 26, 1997; PTO 892) and WO 97/24139 publication (newly cited, published ; PTO 892) or Rabjohn et al (of record, J Clin Invest 103(4): 535-542, Feb 1999; PTO 1449) as applied to claims 34-36, 38-40, 43-44 and 48-49 mentioned above and further in view of Leclerc et al (of record; J Immunology 144(8): 3174-3182, 1990; PTO 892).

The combined teachings of the US application 2005/0175630 A1, the '311 patent and the WO 97/24139 publication or Rabjohn et al have been discussed supra.

The invention in claim 42 differs from the teachings of the references only in that the composition wherein the modified allergen is located in the periplasm instead of in the cytoplasm.

Leclerc et al teach the use of heat-killed *E coli* as a pharmaceutical carrier. Leclerc et al teach a method of providing a composition comprising dead recombinant *E coli* that have produced an antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm using expression vector pPD178 or pPD65 based on mutant derivatives of the periplasmic maltose binding protein of *E coli* known in the art (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach immunization with dead bacteria expressing the antigen in periplasm induces high levels of poliovirus or hepatitis specific antibodies (see page 3175, left col., second full paragraph, page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce modified peanut allergen in the periplasm by substituting the vector or plasmid in *E coli* that has produced modified peanut allergen Ara h1, Ara h2 or Ara h3 in the cytoplasm of the US application 2005/0175630 A1, the '311 patent and the WO 97/24139 publication or Rabjohn et al for the vector pPD178 or pPD65 in *E coli* that have produced antigen in the periplasm as taught by Leclerc et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to produce modified peanut allergens in the periplasm because Leclerc et al teach administering dead bacteria expressing the antigen in periplasm induces high levels of specific antibodies (see page 3175, left col., second full paragraph, page 3177, col. 1, Figure 3, Table II, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to use non-secreted *E coli* as allergen delivery system because it is common sense to shield the highly anaphylactic peanut allergen as taught by the WO 97/24139 publication or Rabjohn et al from the immune system until it is engulfed by antigen presenting cells known to any one of ordinary skill in the immunology or vaccine art.

One having ordinary skill in the art would have been motivated with the expectation of success to modified peanut allergen Ara h1 or Ara h2 because mutated peanut allergen that has reduced IgE binding would be useful for treating highly anaphylactic peanut allergy in human as taught by the WO 97/24139 publication (See claim 32 of the publication, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to modified peanut allergen Ara h3 because modified peanut allergen Ara h3 that has reduced IgE binding as compared with the wild-type peanut allergen Ara h3 has the therapeutic potential for treating peanut allergy as taught by Rabjohn et al (see abstract, in particular).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-36 and 38-49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-45 of copending Application No. 12/843,739. Although the conflicting claims are not identical, they are not patentably distinct from each other because issuance of a patent to instant application drawn to a *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen such as peanut allergen Ara h1, Ara h2, Ara h3 and Ara h6 has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the modified allergen is located in the cytoplasm or periplasm of the dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol would include the pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: l, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 12/843,739.

Thus the issuance of a patent to instant application (genus) would include the pharmaceutical composition of 10/728,051 (specie). The issuance a patent to copending application 10/728,051 (species) anticipates the claimed composition of instant application (genus).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
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